REMARKS

Reconsideration of the subject application is requested in view of the foregoing amendments and the following remarks.

Claims 1-7, 9, 10, 12-15, 17-21, 23 and 29 are pending in the application, with claims 1, 9, 12-15, 19, 20-21 and 29 being independent. Claims 22, 24-26 have been cancelled without prejudice to or disclaimer of the subject matter recited therein. Claims 1, 12 and 19-21 have been amended. Claim 29, which recites the compound IIIa-14 that is disclosed in the specification, has been newly added. Support for the amendments to the claims may be found in the original specification, for example, on pages 28-29 in connection with claim 1 and page 24 in connection with claim 12. No new matter has been added.

Claim objections

The Examiner has indicated that should claim 21 be found allowable, claim 19 will be objected to under 37 C.F.R. §1.75 as being a substantial duplicate thereof. Applicants submit that these claims are not substantial duplicates of one another.

The regulation at 37 C.F.R. §1.75 states:

> Nevertheless, when two claims in an application are duplicates, or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other claim under 37 CFR 1.75 as being a substantial duplicate of the allowed claim.
>
> (emphasis added)

Claim 19 recites "[a] method of inhibiting GSK-3 activity in a patient", whereas claim 21 recites "[a] method of treating a GSK-3 mediated disease" in which a "therapeutically effective" amount of the relevant compound is administered to a patient "in need thereof." The latter two elements, which are recited in claim 21, are not recited in claim 19. Applicants submit that, at least for this reason, claims 19 and 21 are not substantial duplicates of one another, and respectfully request that the Examiner withdraw the relevant objection.

The Examiner has also objected to claims 20 and 22 as being substantial duplicates of each other as discussed in 37 C.F.R. §1.75. Without conceding the propriety of this objection,

and to expedite prosecution of the present application, Applicants have canceled claim 22 without prejudice or disclaimer.

The Examiner has objected to claims 19-22 because of the informality comprising recitation of the abbreviation "AML" instead of "ALS" to designate amyotrophic lateral sclerosis. Without conceding the propriety of this objection, and to expedite prosecution of the present application, Applicants have amended claims 19-21 to recite "ALS" instead of "AML." Claim 22 has been canceled as discussed immediately above.

Statutory double patenting rejection

Claims 1-7, 9-10, 12-13 and 24-26 were rejected under 35 U.S.C. §101 as claiming the same invention as that of claims 1-7, 9-10, 12-13 and 19-21 of U.S. Patent No. 6,664,247. The Examiner further stated that if the present claims were amended to recite "pharmaceutically acceptable salt . . . to overcome the enablement rejection, then claim 1 would be of the same scope as reference claim 1" of the '247 patent. Applicants in the current Response have amended claim 1 to recite "pharmaceutically acceptable salt." However, Applicants submit that the statutory double patenting objection is nevertheless not proper.

MPEP §804 enunciates the test for statutory double patenting:

> A reliable test for double patenting under 35 U.S.C. 101 is whether a claim in the application could be literally infringed without literally infringing a corresponding claim in the patent. *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970). Is there an embodiment of the invention that falls within the scope of one claim, but not the other? If there is such an embodiment, then identical subject matter is not defined by both claims and statutory double patenting would not exist. For example, the invention defined by a claim reciting a compound having a "halogen" substituent is not identical to or substantively the same as a claim reciting the same compound except having a "chlorine" substituent in place of the halogen because "halogen" is broader than "chlorine."

Applicants submit that because claim 1 of the present application has differing scope from claim 1 of the '247 patent, claim 1 of the present application should not be rejected for statutory double patenting, based on the standard set forth in MPEP §804. Claim 1 of the present application explicitly recites specific optional substituents of the recited C6-10 aryl, the heteroaryl ring having 5-10 ring atoms, the C1-6 aliphatic, and the heterocycle ring having 5-10 ring atoms. In contrast, claim 1 of the '247 patent contains no such recitation. Applicants

submit that the explicitly recited specific optional substituents in claim 1 of the present application and the absence of such a recitation in claim 1 of the '247 patent mean that the scopes of the two claims are different under the test enunciated at MPEP §804. For this reason, Applicants respectfully request that the statutory double patenting rejection of claim 1 of the present application be withdrawn.

Claims 24-26 have been canceled as discussed earlier. Claims 2-7, 9-10 and 12-13 of the present application each depend from claim 1, which is currently the only independent claim of the present application. Because a statutory double patenting rejection of claim 1 of the present application is not proper in connection with claim 1 of the '247 patent as discussed above, the rejections of claims 2-7, 9-10 and 12-13 of the present application are also not proper over the relevant claims of the '247 patent identified in the present office action, since each of these latter claims depends from claim 1 of the '247 patent. Therefore, Applicants respectfully request that the statutory double patenting rejections of claims 2-7, 9-10 and 12-13 of the present application also be withdrawn.

Obviousness-type double patenting rejection

Claims 1-7, 9-10, 12-15 and 17-26 have been rejected under the judicially created doctrine of obviousness-type double patenting over claims 1-23 of U.S. Patent No. 6,664,247. Claims 22 and 24-26 have been canceled as discussed earlier. Without conceding the propriety of this rejection, Applicants are, in order to expedite prosecution of the present application, submitting a terminal disclaimer together with the present Response and disclaiming any term of a patent issuing from the present application that is in excess of the term of U.S. Patent No. 6,664,267. Applicants submit that the double-patenting rejection of claims 1-7, 9-10, 12-15, 17-21 and 23 will be overcome upon submission of the terminal disclaimer.

Provisional double patenting rejection

Claims 1-7, 9-10, 12-15 and 17-18 have been provisionally rejected under the judicially created doctrine of obviousness-type double patenting over claims 34-56 of U.S. Application No. 11/500,981. Without conceding the propriety of the provisional rejection,

Applicants respectfully request that the rejection be held in abeyance until either the present application or U.S. Application No. 11/500,981 is deemed to be in condition for allowance.

Applicants note that the Examiner has maintained the provisional rejection in the previous office action dated February 13, 2006 of claims 1-7, 9-10, 12-15 and 17-18 based on obviousness-type double patenting in light of claims 34-36 of U.S. Application No. 10/464,430. Applicants had in their Response dated August 3, 2006 requested that these rejections be held in abeyance until either the present application or U.S. Application No. 10/464,430 is placed in condition for allowance. Applicants maintain their request for abeyance.

Rejections under 35 U.S.C. §112, first paragraph

A. Claims 1-7, 9-10, 12-15 and 17-26

The Examiner rejected these claims under 35 U.S.C. §112, first paragraph, because of his finding that the specification, while being enabling for a compound of formula IIIa or a pharmaceutically acceptable salt thereof, does not reasonably provide enablement for a pharmaceutically acceptable derivative or prodrug of formula IIIa. The Examiner suggested that the recitation of "pharmaceutically acceptable derivative or prodrug" be replaced with "pharmaceutically acceptable salt" in all relevant claims.

Without conceding the propriety of the rejection and solely to expedite prosecution of the present application, Applicants have amended claim 1 to recite "pharmaceutically acceptable salt" in place of "pharmaceutically acceptable derivative or prodrug." Applicants submit that this amendment should overcome the Examiner's currently discussed rejections of claims 1-7, 9-10, 12-15, 17-26 under 35 U.S.C. §112, first paragraph.

B. Claims 12-14 and 24-26

The Examiner rejected these claims under 35 U.S.C. §112, first paragraph because of his finding that the specification, while being enabling for a method of treating diabetes, does not reasonably provide enablement for a method of inhibiting Aurora-2, GSK-3, or Src activity in a biological sample, or a method of inhibiting Aurora-2 activity in a patient, or a method of enhancing glycogen synthesis or lowering blood glucose in a patient, or a method of inhibiting the production of hyperphosphorylated Tau protein in a patient, or a method of inhibiting the

phosphorylation of β-catenin. The Examiner provided a large number of unrelated rationale in support of this conclusion. Applicants respectfully submit that the office action is not clear in relating each of these rationale to the conclusion of non-enablement; nevertheless, this Response discusses and responds to each of these in turn below.

Without conceding the propriety of the currently discussed rejections and solely to expedite prosecution of the present application, Applicants have canceled claims 24-26. For that reason, the discussion below focuses on claims 12-14.

The contention that claims 12-14 are "reach through" claims

The Examiner contends that claims 12-14 are reach-through claims, and states that such claims "in general have a format drawn to mechanistic receptor binding or enzymatic funcationality and thereby reach through to the corresponding therapeutic method of any or all diseases, disorders or conditions, for which they lack written description and enabling disclosure in the specification thereby requiring undue experimentation for one of skill in the art to practice the invention."

Applicants respectfully disagree with the Examiner's contention that claims 12-14 are reach-through claims. First, none of these claims are directed to or even recite either "mechanistic receptor binding" or "enzymatic funcionality."

Second, the definition and examples of reach-through claims set forth in publicly available material at the PTO also indicate that claims 12-14 are not reach-through claims. The joint report of the PTO, EPO and JPO dated November 5-9, 2001 entitled "Report on comparative study on biotechnology patent practices; Theme: comparative study on reach-through claims, prepared as part of the Trilateral Project B3B (available at http://www.trilateral.net/projects/biotechnology/reach_through_claims/B3b_reachthrough_text.pdf), defines reach-through claims as being claims to future inventions based on currently disclosed inventions. The examples provided of reach-through claims in that document that were found to not satisfy the enablement criteria of the PTO illustrate this definition: (i) an isolated

and purified receptor sequence, where the specification does not disclose the function of the receptor; (ii) a method of identifying a compound that acts as an agonist of a receptor by screening the compound by contacting it with a cell expressing the receptor on its surface, where the specification does not provide any guidance regarding the activity of the receptor or working examples; (iii) a compound identified by the screening; (iv) a method of treatment using the compound identified by such screening; (v) a method of treatment of an unidentified disease by a compound disclosed in the specification as identified using the screening process, (vi) a claim to a monoclonal antibody which recognizes a receptor, where the specification does not provide any guidance regarding the activity of the receptor or working examples.

Similarly, guidance material available at the web site of the PTO (see, e.g., presentation entitled "Patentability of Reach-Through Claims" by Jose G. Dees, Supervisory Patent Examiner, Art Unit 1616, available at http://www.uspto.gov/web/patents/biochempharm/documents/patreachclaim.pps) provides the following examples of reach-through claims: (a) small molecule per se claim, where the molecule is defined as binding to a target, but is not otherwise identified; (b) method of screening claim for molecules that bind to a target that are not otherwise identified; and (c) method of treating a disease by a compound not defined by any structure but by its ability to bind to a target.

In each of the cases discussed in the materials of the PTO, the claimed element either lacks a definition of structure (e.g., case (iii) in which an unknown compound is claimed based on its activity with a target), or a definition of function (e.g., case (v) in which a method of treating an unidentified disease is claimed based only on its being responsive to a particular compound.)

None of claims 12-14 share these features, and are therefore not reach-through claims. Claim 12 is directed to a method of inhibiting Aurora-2, GSK-3 or Src activity in a biological sample comprising the step of contacting the biological sample with a compound which has the structure of any of claims 1-7. The specification discloses that each of Aurora-2, GSK-3 and Src activity takes place in biological systems. See, e.g., page 2, line 24 - page 3, line

3 disclosing that Aurora-2 is a kinase that has been implicated in human cancer; page 3, line 4 - page 5, line 30 disclosing that GSK-3 has been identified in several human diseases; and page 22, lines 12-32 disclosing that Src has been implicated in a variety of diseases as described in references accessible to those of ordinary skill in the art. The specification further discloses that compounds of claims 1-7 have the effect of inhibiting Aurora-2, GSK-3 and/or Src activity in biological systems. See, e.g., page 311, line 9 - page 320, line 30. Thus, there is no unidentified function or structure in claim 12 in the sense of the reach-through claims set forth in the guidance documents of the PTO. Therefore, claim 12 is not a reach-through claim.

Similarly, each of claims 13 and 14 disclose inhibiting Aurora-2 activity in a patient by administering a compound that has the structure of the compounds in claims 9 and 10, respectively. As stated above, the specification discloses that Aurora-2 has been implicated in human diseases, and the specification further discloses that the compositions of claim 9 have been shown to inhibit Aurora-2 activity. Thus, there is no unidentified function or structure in claims 13 and 14 in the sense of the reach-through claims set forth in the guidance documents of the PTO. Therefore, claims 13 and 14 are not reach-through claims.

The contention that there is insufficient guidance regarding the assay

The Examiner has stated that the specification lacks sufficient guidance in connection with the testing assays provided at pages 311-320 of the specification. In this connection, the Examiner first states that "all compounds for which the activity related to some of the kinase inhibition is indicated, are structurally distinct from the instant claims, i.e., the activity is reported to compounds wherein ring A is pyrimidinyl group as compared to the instant claims wherein ring A is pyridinyl." The Examiner is mistaken. Among the compounds of series IIIa, (i) which are exemplified in the specification on pages 117-122, (ii) which are recited in claims 12-14 through the dependence of these claims from independent claim 1, and (iii) for a subset of which specific kinase inhibiting activity is disclosed on pages 311-320, only compounds IIIa-52, IIIa-57 and IIIa-60 contain pyridinyl groups; however, these compounds also contain the pyrimidinyl group that is common to all series IIIa compounds and that is also part of formula IIIa as recited in claim 1. For that reason, Applicants respectfully assert that the Examiner is

mistaken in his claim that the compounds for which activity related to kinase inhibition is indicated are structurally distinct from the compounds of the instant claims.

The coupled enzyme system of Fox et al.

The Examiner asserts that the article by Fox et al. entitled "A single amino acid substitution makes ERK2 susceptible to pyridinyl imidazole inhibitors of p38 MAP kinase", 7 Protein Science 2249-55 (1998), which the specification on pages 311-320 cites as an example of the coupled-enzyme system technique, relates to inhibition of p38 MAP kinase activity. Although there is no explicit statement, the Examiner appears to be implying that the disclosure of Fox cannot be cited to provide support for the present application's statements about the coupled-enzyme system discussed in the biological testing section of the application at pages 311-320 in connection with kinases differing from p38 MAP.

The article by Fox et al. on page 2253-54 describes the coupled spectrophotometric assay that was used to measure the kinase activity of p38 MAP kinase. Although this disclosure in the Fox article relates to measurements for p38 MAP kinase, which differs from the Aurora-2, GSK-3 and Src kinases of claims 12-14, the coupled-spectrophotometric assay technique is a common technique for measuring kinase activity for kinases other than p38 MAP kinase. Furthermore, the Examiner has not cited any evidence that suggests that the coupled spectrophotometric assay technique of the Fox paper is only suitable for measuring kinase activity of p38 MAP kinase, and that it would not work for measuring kinase activity of Aurora-2, GSK-3 and Src. Applicants submit, in the absence of any such showing, that the enablement rejection based on the Examiner's finding that the Fox paper does not relate to Aurora-2, GSK-3 and Src kinases of claims 12-14 is in error and should be withdrawn.

The correlation with efficacy in biological samples and use for the various purposes wherein inhibition activity is useful

The Examiner states that "applicant has not provided how this correlates with the efficacy in all types of biological samples encompassed by the instant method and their use in the various purposes wherein the inhibition activity is useful." Although this statement is not

entirely clear, the Examiner appears to be stating that there is a lack of correlation between the assays disclosed in pages 311-320 of the application (discussing the inhibition activity of the compounds in Aurora-2, GSK-3 and Src assays) and either of (i) efficacy in biological systems and (ii) efficacy for the purposes for which inhibition activity is useful. The Examiner provides specific examples for which, in his opinion, the specification does not enable the claimed inhibition activity: blood transfusions and organ transplantations.

Applicants respectfully disagree with the Examiner. Claim 12 is directed to a method of inhibiting Aurora-2, GSK-3 or Src activity in a biological sample comprising the step of contacting the biological sample with a compound which has the structure of any of claims 1-7. As discussed above, the specification discloses that each of Aurora-2, GSK-3 and Src activity takes place in biological systems. The specification further discloses that compounds of claims 1-7 have the effect of inhibiting Aurora-2, GSK-3 and/or Src activity in biological systems. See, e.g., page 311, line 9 - page 320, line 30. Applicants submit that these disclosures provide proper support for the claim elements actually recited in the claims.

Applicants further point out that the Examiner has not related his discussed examples of blood transfusions and organ transplantations to the language of claim 12. In particular, it is not clear how or even whether the Examiner is reading claim 12 on blood transfusions and organ transplantations. Applicants submit that this claim should not be rejected for enablement based on an alleged lack of enablement of the Examiner's examples, in the absence of a showing of a nexus between the Examiner's examples and the claim.

Additionally, claim 12 has, without conceding the propriety of any rejection and for the sole purpose of expediting prosecution of the present application, been amended to recite that it applies to in vitro inhibition of the relevant kinases. Support for this amendment appears at page 24, lines 5-10 of the specification. Applicants submit that the disclosures discussed in the paragraph immediately above fully support and enable claim 12 as amended.

Each of claims 13 and 14 discloses inhibiting Aurora-2 activity in a patient by administering a compound that has the structure of the compounds in claims 9 and 10,

respectively. As discussed earlier, the specification discloses that Aurora-2 has been implicated in human diseases, and the specification further discloses that compounds of the compositions of claim 9 have been shown to inhibit Aurora-2 activity. Applicants submit that these disclosures provide proper support for the claim elements actually recited in claims 13 and 14.

Applicants further point out that the Examiner has not related his discussed examples of blood transfusions and organ transplantations to the language of claims 13 and 14. In particular, it is not clear how or even whether the Examiner is reading these claims on blood transfusions and organ transplantations. Applicants submit that these claims should not be rejected for enablement based on an alleged lack of enablement of the Examiner's examples, in the absence of a showing of a nexus between the Examiner's examples and these claims.

Statement that the instant claims read on many therapeutic methods

The Examiner states that "the instant claims read on many therapeutic methods, for example a method of treating cancer, Alzheimer's disease, autoimmune diseases, etc." The Examiner then states that because no compound has been found to treat cancers of all types generally, the claim must not be enabled. Applicants respectfully disagree with the Examiner and request that the rejection be withdrawn.

MPEP §2164 sets forth the standard for assessing compliance with the enablement requirement. It in particular states that "[t]he invention that one skilled in the art must be enabled to make and use is that defined by the claim(s) of the particular application or parent. (Emphasis added.)

Claims 12-14 recite methods of inhibition, not methods of curing or effectively treating cancer. In particular, none of claims 12-14 recites a method for curing or effectively treating cancer, or any of the other diseases discussed by the Examiner in the relevant section of the present office action. In fact, these claims do not even recite any specific diseases. Based on the standard set forth at MPEP §2164, assessing enablement of claims 12-14 on the basis of

elements not recited in those claims would be improper. Therefore, Applicants respectfully request that the Examiner withdraw his enablement rejection of these claims.

Statement regarding alleged non-disclosure of identification of patients in need of treatment requiring the specific kinase

The Examiner states that there is no disclosure regarding how a patient in need of treatment requiring the specific kinase inhibiting activity is identified, and further, how all types of diseases having diverse mechanisms are treated.

Claims 12-14 do not contain the limitation of a patient "in need of" treatment. For that reason, enablement of these claims should not require disclosure of identification of patients in need of specific treatments. See MPEP §2164, excerpted above.

Claims 24-26, each of which did contain such a limitation, have been canceled without conceding the propriety of their rejection to expedite prosecution of the present application. For that reason, Applicants submit that this basis for the currently discussed enablement rejection is now moot and that the rejection should therefore be withdrawn.

Statement regarding the unpredictability of the therapeutic approach based on kinase inhibiting activity

As stated in the section immediately above, none of claims 12-14 recites a method of treatment directed to a specific disease, and claims 24-26, which did recite methods of treatment directed to specific diseases, have been canceled without conceding the propriety of their rejection to expedite prosecution of the present application. For that reason, the current basis for rejecting the claims for lack of enablement is also moot and the corresponding rejections should therefore be withdrawn.

Applicants submit, however, that the evidence provided by the Examiner in this connection does not indicate the unpredictability of therapeutic approaches based on kinase inhibiting activity. The Examiner, in particular, stated:

> How sister kinetochores attach to microtubules from opposite spindle poles during mitosis (bi-orientation) remains poorly understood", see Tanaka et al. (PubMed Abstract enclosed.) Also, Rogers et al., express that "How the selective release of chromosome cohesion is regulated during meiosis remains unclear." This is clearly indicative of the fact that the therapeutic role of kinase inhibitors is very speculative.

These statements at most indicate that certain specific details relating to the function of the relevant kinases are not yet entirely understood. Nevertheless, as discussed in the specification of the present application, these kinases have been implicated in a number of specific diseases. See, e.g., the discussion relating to Aurora-2 on pages 2-3 of the present application that cites authority to the effect that (i) the kinase is believed to be involved in protein phosphorylation events that regulate the cell cycle, (ii) misregulation of the cell cycle can lead to cellular proliferation and other abnormalities; and (iii) the Aurora-2 protein has been found to be overexpressed in tissue afflicted with specific forms of cancer. Applicants submit that such a disclosure may most certainly provide basis for enablement of a claim directed to a particular therapeutic approach relating to a specific disease.

Applicants also submit that the specification of the present application provides disclosure relating to pharmaceutical use of the relevant compounds; see, e.g., pages 28-31 of the present application.

Statement regarding specific and substantial utility

The Examiner directs Applicants attention to the "Revised Utility and Written Description Guidelines, at 66 FR 1092-1099, 2001" regarding the requirement that "a claimed invention must have a specific and substantial utility." Applicants note that the Examiner has not made any rejection based on the utility requirement of U.S. Patent Law at 35 U.S.C. §101. Furthermore, the United States Court of Appeals for the Federal Circuit has enunciated a standard in a case with facts similar to the facts of the present application (in particular the assays discussed at pages 311-320) that is clearly satisfied in the current application:

> We perceive no insurmountable difficulty, under appropriate circumstances, in finding that the first link in the screening chain, *in vitro*

> testing, may establish a practical utility for the compound in question. Successful *in vitro* testing will marshal resources and direct the expenditure of effort to further *in vivo* testing of the most potent compounds, thereby providing an immediate benefit to the public, analogous to the benefit provided by the showing of an *in vivo* utility.
>
> Cross v. Iizuka, 753 F.2d 1040 (Fed. Cir. 1985) (discussed at MPEP Section 2107.01(III))

For these reasons, Applicants submit that to the extent the Examiner has made a rejection of claims based on the utility requirement of 35 U.S.C. §101, that rejection should be withdrawn.

Conclusion

In view of the above, Applicants submit that the subject application is in condition for allowance. Favorable consideration and passage to issue of the application are respectfully requested.

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Respectfully submitted,

By _____

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